



GlaxoSmithKline

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**Re: Comments on Draft Guidance for Industry on the Clinical Evaluation of Weight-Control Drugs -
Docket No. 2003D-0570 (Federal Register Notice 26 January 2004 [Vol. 69, No. 16])**

Dear Sir or Madam::

GlaxoSmithKline (GSK) supports the Food and Drug Administration's (FDA's) initiative to facilitate development and availability of innovative medical products by updating its 1996 Draft Guidance for Industry entitled, "*Guidance for the Clinical Evaluation of Weight-Control Drugs.*" In response to FDA's solicitation for public input prior to republication of the guidance as a draft, this submission provides the collective response on behalf of GlaxoSmithKline (GSK).

Since the Agency issued the draft guidance on September 24, 1996, overweight and obesity have become more readily recognized as a disease that is associated with morbidity and early death. In a recently published paper in *JAMA* (2004; 291:1238-1245), poor diet and physical inactivity accounted for 400,000 deaths (16.6%) in United States in the year 2000. This is second only to smoking, the current leading cause of death (435,000 deaths; 18.1%). Based on current trends, it is estimated that that poor diet and physical inactivity will soon overtake tobacco as the leading cause of death. These statistics underscore the urgent need to more adequately address the growing epidemic of overweight and obesity in this country. For millions of Americans, efforts to promote lifestyle modification as the primary means to a healthy weight have failed. For these individuals, there is a significant unmet medical need for safe and effective pharmacological treatment options. We acknowledge the efforts of the FDA's Obesity Working Group to address the major public health problem of obesity through its ongoing collaborative activities involving scientific experts from organizations such as the American Obesity Association (AOA), National Institutes of Health (NIH), and the pharmaceutical industry.

In the attached document, we have made a number of proposed specific changes to FDA's 1996 draft guidance. Provided on the following pages, is an overview of some key elements of the changes we have included in GSK's proposal for an updated guidance.

2003D-0570

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Key Elements

Lines 1 - 2

We recommend a modification in the title of the guidance to read, "*Guidance for the Clinical Evaluation of Drugs for the Treatment of Overweight and Obesity*."

Lines 18 - 58

Section 2, General Rationale. Since the initial release of the draft guidance in 1996, there has been a significant body of literature published on the deleterious effects associated with excess weight (i.e., overweight and obesity). Excess weight has now become an alarming epidemic in both the adult and pediatric populations and may soon become the leading cause of mortality. As such, we feel that it is important to more accurately reflect excess weight as a disease and acknowledge the multifactorial nature of its etiology. We have provided suggested language to reflect the severity of this burden and have stressed the importance of being able to provide pharmacological treatment options. Examples also have been provided as to how overweight and obesity can be measured, and acknowledgment has been made that certain groups have increased health risks at the currently accepted body mass index (BMI) definitions for overweight and obesity.

Lines 59 - 79

Section 3, Potential Therapeutic Indications. Because overweight and obesity are affected by a variety of contributing factors, we suggest that the guidance identify a range of possible clinically meaningful benefits of drugs to treat excess weight, including the following indications, which will be discussed in greater detail in subsequent sections of the document:

1. Reduction in weight (i.e., percentage weight loss)
2. Improvement in body-fat composition (i.e., reduction in the proportion of adipose tissue)
3. Sustained weight reduction (i.e., weight-loss maintenance / prevention of regain)
4. Prevention of weight gain associated with other effects (e.g., occurring with use of certain medications or during smoking cessation)

Lines 80 - 103

Section 4, Population. We believe that for the intended use, the guidance should encourage the assessment of the drug in an appropriately diverse patient population (demographics, concomitant drug use, etc.).

In recognition of the significant public health threat to children and adolescents, the guidance should encourage initiation of pediatric studies as early as practicable, when a therapeutic benefit is anticipated. The guidance, however, should not include any requirements for pediatric data that might delay the availability important new treatments for adults.

We feel that sponsors should be able to define the study population in support of a specific, desired indication. If a sponsor chooses to pursue an indication in patients who fall outside of the recommended BMI attributes (e.g., ethnic groups who may be at higher risk at lower BMIs) or places a focus on specific subpopulations, an appropriate justification should be provided and agreement reached with the Agency. We believe that the primary goal should be to make new treatment options available as soon as possible to those who can most benefit. As such, the Agency should not require evaluation of a new drug in all possible patient groups prior to initial approval. The sponsor should provide justification for the specific population(s) it has targeted for the intended use. If necessary, a description of measures that sponsors would take to facilitate the intended use of the drug may be requested.

We recommend a change in Line 77 of the original draft guidance from "Methods used to recruit subjects for obesity drug trial should be noted" to "Inclusion and exclusion criteria for enrolling subjects for obesity trial should be noted to support the indicated population."

Lines 104 - 112

Section 5, Phase 1 Studies. We recommend that this section be renamed from the previous heading, "Early Clinical Trials" to "Phase 1 Studies." We have maintained the spirit of the original wording in this section, which provides a brief description of the purpose of these studies (e.g., safety, tolerability, and possible pharmacodynamic profiling). A recommendation is made to conduct such studies as randomized, double blind and placebo controlled, but the recommendation should not preclude the sponsor from conducting open-label or single-blind studies.

Lines 113 - 125

Section 6, Phase 2 Studies. We recommend that this section be renamed from the previous heading, "Dose Range Finding" to "Phase 2 Studies." Likewise, we have maintained the spirit of the original wording in this section, which provides a brief description of the purpose of these studies (e.g., safety, efficacy, and dose-response evaluation in the target population). Because there are numerous means by which to provide dietary and activity regimens, we believe that the guidance should not be restrictive in these areas. We have thus recommended that standardized dietary and activity regimens should be provided, as appropriate for the indicated patient population, within a trial. This will permit a sponsor to design the clinical trial with greater flexibility in regard to inclusion of the type of lifestyle modification as well as to provide a holistic approach for the study participant.

Lines 126 - 146

Section 7, Phase 3 Studies. We recommend that this section be renamed from the previous heading, "Trials to Establish Efficacy" to "Phase 3 Studies." Although the general spirit of the original wording within this section and its subsections has been maintained, we believe that there should be no inclusion of a run-in period, because this does not always reflect the real-world situation, and it may confound the interpretation of data. We advocate an holistic approach by providing an accompanying standardized lifestyle modification

within a given trial that would suit the desired indicated population. We have provided suggested wording to encourage evaluation of diverse populations for the intended use (e.g. demographics, concomitant diseases, etc). The population should be defined to support a given indication / claim, and, if so desired, a sponsor could also include an active control.

Lines 147 - 208

Section 7.1, Endpoint Evaluation. Because overweight and obesity are affected by a variety of contributing factors, we suggest that the guidance identify a range of possible clinically meaningful benefits of drugs to treat excess weight. In addition, as new agents become available, there is the potential to add onto pre-existing therapy or to use two agents together as an initial approach to weight control, especially if the pharmacological mechanisms of action are complementary. The design for the respective treatment approaches could potentially differ, and the sponsor is encouraged to consult the Reviewing Division on the proposed clinical study design to support any or all of the following indications / claims:

1. **Reduction in weight (i.e., percent weight loss); Section 7.1.1** Lines 155 - 168; We concur with the draft guidance's original criteria for approval.
2. **Improvement in body-fat composition (i.e., reduction in the proportion of adipose tissue); Section 7.1.2,** Lines 169 - 175. Because a favorable change in body composition may not necessarily be accompanied by a decrease in weight (sometimes there may be an increase due to an increase in muscle mass) we believe that a sponsor could also seek approval based on a favorable change in body-fat composition. At this time, however, we cannot recommend quantitative recommendations, but these could be developed, with appropriate input provided from scientific experts via a public consensus meeting.
3. **Sustained weight reduction (i.e., weight-loss maintenance / prevention of regain); Section 7.1.3,** Lines 176 - 186. We feel that a sponsor could also obtain an indication based on the demonstration of maintenance of prior weight loss / prevention of the weight regain. This demonstration can be independent from having to demonstrate weight loss with the same therapy. The means by which weight loss had been achieved, however, must be standardized within a given study (e.g., responders on prior drug therapy [monotherapy or combination therapy] or responders on a specified weight-loss program, such as Weight Watchers).
4. **Prevention of weight gain associated with other effects (e.g., occurring with use of certain medications or during smoking cessation); Section 7.1.4,** Lines 187 - 191. We believe that there are certain populations that may become more susceptible to weight gain and, as such, as sponsor could obtain approval based on the prevention of weight gain in such populations.

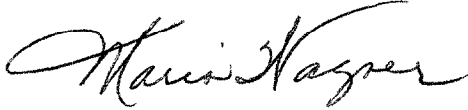
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We appreciate the opportunity to provide our input and look forward to the Agency's continued efforts to facilitate development of safe and effective treatment options to address the significant health threat posed by overweight and obesity.

Sincerely,

A handwritten signature in cursive script, appearing to read "Maria Wagner".

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GUIDANCE FOR THE CLINICAL EVALUATION OF DRUGS FOR THE TREATMENT OF OVERWEIGHT AND OBESITY

1. INTRODUCTION

This guidance is intended to recommend clinical trials and clinical drug development programs that will provide acceptable demonstrations of the safety and efficacy of drugs to treat overweight and obesity. General guidelines for conduct of clinical trials and for development of new drugs for marketing should be followed in developing such drugs. Only those aspects of the trials that are specific to such drugs will be discussed in this document. Refer particularly to the Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications.

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

2. GENERAL RATIONALE

Obesity is a long-term, chronic, and relapsing disease in which the principal sign is excess adipose tissue resulting from imbalance in energy expenditure and energy intake. It is a multifactorial disease in which gender, race, genetic, metabolic, environmental and behavioral factors can contribute, and it is affected by powerful neuroendocrine factors that affect both hunger and satiety. Excess weight alone causes a number of changes in the body's lipids and hormonal activity, and obesity significantly affects the musculoskeletal and cardiovascular systems. Obesity is associated with significant morbidity and premature death, and it has become a serious public health problem in the United States, reaching epidemic proportions in adults, children, as well as the elderly. Over 25% of adult Americans are obese, and the percentage of obese can be much higher

in some subpopulations. The adult population with morbid or severe obesity (approximately 100 pounds overweight or a Body Mass Index [BMI] > 40) is nearly 9 million persons.

Obesity is well established as a cause of many important comorbid conditions, including some cancers, stroke, heart disease, hypertension, hypercholesterolemia, osteoarthritis of the knee and hip, and type 2 diabetes. In addition, obesity is strongly associated with other adverse health conditions such as gall bladder disease, sleep apnea, depression and low self-esteem. Lack of physical activity and poor nutrition account for approximately 400,000 deaths each year, making these risk factors currently second only to tobacco use in causes of preventable death (CDC Study, *Actual Causes of Death in the United States, 2000*; *JAMA* (2004) 291:1238-1245). Extrapolation of these data suggest that the lack of physical activity and poor nutrition will likely surpass tobacco use as the number one cause of preventable death. With the rising rate of obesity and the resulting consequences for chronic conditions and potentially death, it is a public health imperative to develop effective measures to help patients maintain a healthy weight. For those patients for whom appropriate nutrition and behavioral changes have proven ineffective, there is a significant unmet medical need for safe and effective medications. Development of pharmacological treatment options is a critical priority as part of an innovative approach to helping Americans achieve a healthy weight.

Obesity may be measured in several acceptable ways. Surrogate measures include excess pounds over a healthy weight, waist circumference, BMI, or waist-to-hip ratio. The National Institutes of Health, the Centers for Disease Control and Prevention and the World Health Organization have used the BMI scale. According to generally accepted cutoff points, the BMI for overweight is defined as equal to or greater than 25 to 29.9, obesity as 30 to 39.9 and severe or morbid obesity as 40 or greater. There are some select populations (e.g., Asian), however, that have been shown to have increased health risks associated with overweight / obesity at lower BMI values. BMI does not distinguish size that is due to bone and muscle from that due to fat, nor does it identify subjects with visceral obesity, a potent predictor of morbidity. Drug developers may use any scientifically acceptable measurement definition.

3. POTENTIAL THERAPEUTIC INDICATIONS

Obesity is a complex, multifactorial disease that may differ among individuals based on race, ethnicity, genetic difference, or other underlying disorders, and may differ in a given individual across time. In addition, current research indicates that there are distinct physiological systems that contribute to weight loss, weight maintenance and weight gain. Therefore, a therapeutic regimen that might affect one or more of these systems could be considered for registration. Ideally, a successful therapeutic regimen for patients could potentially include any or all of the following indications:

1. Reduction in weight (i.e., percent weight loss)
2. Improvement in body-fat composition (i.e., reduction in the proportion of adipose tissue)
3. Sustained weight reduction (i.e., weight-loss maintenance / prevention of regain)
4. Prevention of weight gain associated with other effects (e.g., occurring with use of certain medications or during smoking cessation)

To achieve one or more of the aforementioned goals, single drugs or drugs in combination may act on one or more mechanisms that affect excess adiposity. These may include reduction of hunger/appetite, enhancement of satiety, alteration in food preferences, enhancement of physical activity, increases in energy expenditure or enhancement of fat oxidation. In addition to the known mechanisms of increased adiposity listed above, a drug may be targeted at novel mechanisms or strategies that at this time are unknown.

4. POPULATION

The supporting clinical program for a potential new drug for treatment of overweight and obesity should include a diverse patient population. Accordingly, within the intended use population, only patients with obvious contraindications should be excluded from Phase 3-study entry. Inclusion of diverse populations would allow for the collection of safety data in important demographic groups such as the elderly, appropriate pediatric populations, patients with concomitant diseases, or patients taking common concomitant

87 medications. Study activities should ensure collection of all pertinent demographic
88 information.

89 Because obesity is a significant public health threat to children and adolescents, when a
90 therapeutic benefit in pediatrics is anticipated, initiation of studies should be initiated as
91 early as practicable.

92 For most overweight and obesity drug studies, subjects in clinical trials should have a
93 body mass index (BMI) of at least 30 for otherwise healthy individuals, and BMI at least
94 27 for those with comorbid conditions (such as, hypertension, hyperlipidemia, glucose
95 intolerance, cardiovascular disease, sleep apnea, or other obesity-related conditions). It is
96 often preferable to identify obesity by methods that measure body fat and its distribution.
97 Inclusion and exclusion criteria for enrolling subjects for obesity trial should appropriate
98 for the targeted population.

99 Drugs that effectively address weight control in overweight patients with a BMI in the
100 range of 25 to 27 may provide a meaningful therapeutic benefit, particularly in those
101 demographic subgroups at increased risk of morbidity. Specific plans to include patients
102 with a BMI in the range of 25 to 27 should be described and justified as part of End of
103 Phase 2 discussions.

104 **5. PHASE 1 STUDIES**

105 For new chemical entities, the earliest clinical trials for safety, tolerability, and
106 pharmacokinetic profiling are usually performed in subjects who are otherwise free of
107 disease. In some instances, pharmacodynamic profiling and dose determination also may
108 be possible.

109 In order to discern adverse effects due to study drug, it is recommended that studies be
110 randomized, double blind and placebo controlled. This does not preclude, however, the
111 conduct of either open-label or single-blind studies; conduct of such studies are at the
112 sponsor's discretion.

6. PHASE 2 STUDIES

Phase 2 trials should be designed to obtain guidance for the design of Phase 3 trials. The goals of Phase 2 studies are to capture information on safety, efficacy and dose response in the target population. The studies should obtain working estimates of the nature and severity of side effects commonly associated with the new product. They should also include a parallel dose-response study across a number of dose levels sufficient for the initial characterization of the dose-response curve for the drug. Patient history may include a number of factors, including family history, alcohol intake, tobacco use, exercise/activity level, dietary habits, comorbidities and concomitantly administered drugs. Dietary and activity regimens should be defined and standardized within a trial and as appropriate for the patient population. Trials should usually be randomized, double blind, and placebo controlled. They should be of sufficient duration to demonstrate preliminary evidence of efficacy and safety.

7. PHASE 3 STUDIES

Trials to establish the safety and efficacy of a drug for the treatment of overweight and obesity should be randomized, double blind, and placebo controlled. Using a range of doses in phase 3 trials could better characterize the relationship between exposure and the resulting clinical benefit and risk, allowing provision of the best dosing advice. In addition, exposure-response data from clinical trials could provide critical information on the need for dose-adjustments in special populations.

To the extent possible, trials should be designed to allow diversity within the target population (e.g., demographics, concomitant illness, co-administered drugs, etc.), and only those patients with obvious contraindications would be excluded from Phase 3 studies. Dietary and activity regimens should be defined and standardized within a trial.

Weight loss achieved with calorie restriction alone is usually associated with loss of both fat and muscle tissue. Exercise has been reported to reduce or eliminate muscle loss. A carbohydrate-restricted regimen will usually result in loss of body water. For these

reasons, it may be desirable in a suitable number of patients, to establish that the subjects have excess body fat by one or more of the accepted measurements, such as skin fold thickness, body circumferences or sagittal diameter, under-water weighing, bioelectric impedance, and DEXA. Such approaches can be used in a subset of the population in the Phase 3 program or perhaps in smaller, pharmacodynamic studies. Follow-up measurements can then confirm if body fat is decreased, commensurate with the weight loss, and that weight loss is not associated with excessive loss of body water or muscle.

7.1 Endpoint Evaluation

In addition to monotherapy, as new agents become available, there is the potential to add onto pre-existing therapy or to use two agents together as an initial approach to weight control, especially if the pharmacological mechanisms of action are complementary. The design for the respective treatment approaches could potentially differ, and the sponsor is encouraged to consult the Reviewing Division on the proposed clinical study design to support any or all of the following indications / claims:

7.1.1 Reduction in Weight (i.e., percent weight loss)

To obtain a monotherapy weight-loss indication, the sponsor should demonstrate at least one of the two following criteria:

- The drug effect is statistically significantly greater than the placebo effect, and the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5%, at the end of one year.

or

- The proportion of subjects who reach a loss of at least 5% of their initial body weight is statistically significantly greater in subjects on drug than those on placebo, at the end of one year.

To obtain a combination therapy indication for weight loss, either as initial therapy or as add-on therapy for patients who would benefit from additional weight loss, the sponsor

should show that the combination provides additional clinical benefit over the individual components and does not result in an unsatisfactory benefit-risk balance.

7.1.2 Improvement in Body-Fat Composition (i.e., reduction in the proportion of adipose tissue)

For monotherapy, the two criteria outlined for a weight-loss indication could also be applied to an indication for the improvement of body-fat composition, using percent of body weight or percent of excess over ideal body weight or change in body mass index. Likewise, the guidance outlined for combination therapy for weight loss could also be applied for an improvement in body-fat composition.

7.1.3 Sustained Weight Reduction (i.e., weight-loss maintenance / prevention of regain)

In order to obtain an indication for sustained weight loss, the sponsor should demonstrate that after a period of prior weight loss, subsequent weight gain is significantly lower in subjects on drug than those on placebo, at the end of one year (i.e., weight rise above the new baseline established following documented weight loss is significantly lower on drug). The means by which weight loss had been achieved must be standardized within a given study (e.g., responders on prior drug therapy [monotherapy or combination therapy] or responders on a specified weight-loss program, such as Weight Watchers). Likewise, it may be possible to apply these criteria for an indication in individuals who have improved their body-fat composition.

7.1.4 Prevention of Weight Gain Associated with Other Effects (e.g., occurring with use of certain medications or during smoking cessation)

In order to obtain an indication for the prevention of weight gain, the sponsor should demonstrate that using either monotherapy or combination therapy, subjects on drug gain significantly less weight than those on placebo, at the end of one year.

Additional Endpoints for Consideration

Changes in parameters associated with risk factors, including measurements of central fat (e.g., waist-to-hip circumference, sagittal diameter, or other direct measures of visceral fat mass) may be appropriate endpoints, depending on the population studied. Delay in the

196 onset of diabetes, osteoarthritis or other complication of obesity and or a positive benefit
197 in the adjunctive treatment of obese patients with these comorbidities may also be a
198 suitable endpoint in certain cases.

199 Measurement of obesity-associated cardiovascular risk factors (e.g., lipids, blood
200 pressure and glucose tolerance) during drug administration is encouraged, as change
201 associated with drug treatment may provide important considerations for
202 prescribers/patients when assessing the expected benefits and risks of potential treatment
203 options. Because the change in such factors are pertinent in making a benefit-to-risk
204 decision for the drug, these findings (positive and negative) should be described in the
205 drug's label.

206 In addition, patient reported outcome (PRO) endpoints should also be considered. These
207 include endpoints of quality of life, patient satisfaction and patient preferences among
208 others.

209 **7.2 Duration of Trials**

210 Pharmacological therapy must be viewed as part of a long-term strategy for weight
211 management. As such, the duration of the clinical trials should be consistent to support
212 the primary efficacy endpoint and intended use of the drug. Pharmacological therapy may
213 be indicated for weight loss and or prevention of weight (re)gain. Depending on the
214 desired indication /claim and overall profile of the drug, it could be possible for a sponsor
215 to submit a marketing application for approval based on safety and efficacy following 12
216 months of exposure in at least 1500 subjects. If necessary, a sponsor's commitment to
217 collect long-term safety data (e.g. 24 months), under actual clinical use conditions, may
218 be required as part of a formal product surveillance program.

219 It is not intended that this Guidance encompass all possible evaluations for overweight
220 and obesity. As the science evolves, opportunities not presented in this guidance may be
221 identified and pursued. Accordingly, other proposed indications will be considered
222 following submission of appropriate scientific rationale to the Division of Metabolic and

223 Endocrine Drug Products. As new drug entities with new modes of action are developed,
224 modifications of the Guidance may become necessary.

225 This document is an informal communication under 21 CFR 10.90(b)(9) that represents
226 the best judgment of the Division of Metabolic and Endocrine Drug Products at this time.
227 This document does not necessarily represent the formal position of the Center for Drug
228 Evaluation and Research or the Food and Drug Administration, and does not bind or
229 otherwise obligate the Center or Agency to the views expressed.

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